National Institute of Allergy and Infectious Diseases
National Institutes of Health

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A Phase II Clinical Trial to Evaluate the Immunogenicity and Safety of a Combined Regimen Using ALVAC-HIV (vCP1452) and AIDSVAX®B/B (HVTN 203)

QUESTIONS AND ANSWERS

1. What is the HVTN 203 Vaccine Trial?

HVTN 203 is a Phase II clinical trial that will examine the safety and immunogenicity of two experimental HIV vaccines, ALVAC-HIV (vCP1452) and AIDSVAX®B/B, given alone or in combination. ALVAC-HIV (vCP1452) stimulates production of cytotoxic T cells (CTLs), which can kill HIV-infected cells, whereas AIDSVAX B/B stimulates production of neutralizing antibodies, which can prevent HIV from infecting cells. By giving the two vaccines together, the investigators aim to stimulate both arms of the immune system. This trial is not large enough to determine if the vaccines tested can prevent HIV infection. That will require studying thousands of individuals in a Phase III trial.

2. Why is the Trial Being Done?

This trial is being conducted so that additional data can be obtained about the safety and immune response of ALVAC-HIV (vCP1452) and this combination vaccine approach. Although other gp120 vaccines have been evaluated in combination with other ALVAC-HIV vaccines, this is the first clinical study to use ALVAC-HIV (vCP1452) and AIDSVAX B/B together. ALVAC-HIV (vCP1452) is the latest generation (most advanced) of the ALVAC-HIV vaccine products and AIDSVAX B/B is re-engineered to stimulate a broader antibody response. This trial will help provide information to determine if this vaccine combination warrants further testing of its effectiveness in preventing HIV infection. Depending on the results of this study, this vaccine combination might be considered for evaluation in a large-scale efficacy trial. Ultimately, the goal of all studies such as this is to obtain information that can be used to help develop a vaccine that can prevent HIVAIDS.

3. Who is Sponsoring the Study?

The study is being conducted through the HIV Vaccines Trials Network (HVTN), which is supported by the National Institute of Allergy and Infectious Diseases (NIAID), a part of the U.S. National Institutes of Health. Since 1987, NIAID has enrolled more than 3,300 men and

women in 53 Phase I and II preventive vaccine trials involving 28 different experimental vaccines. This is the third Phase II HIV vaccine trial sponsored by NIAID.

4. When and Where is the Study Being Conducted?

HVTN 203 will be conducted at 6 to 10 HVTN sites in the United States. The following sites have begun screening volunteers: Vanderbilt University (Nashville, TN), St. Louis University (St. Louis, MO), University of Washington (Seattle, WA), University of Rochester (Rochester, NY), Johns Hopkins University (Baltimore, MD) and University of Alabama (Birmingham, AL). Additional sites in San Francisco, New York City, Boston and Baltimore may be added.

5. Who is Eligible to Participate in the Study?

The study will enroll 330 men and women between the ages of 18 and 60 who are not infected with HIV. Study participants will include individuals whose behaviors place them at low risk for acquiring HIV infection as well as those who participate in higher risk behaviors. Volunteers will receive extensive counseling and support to reduce their risk of HIV infection throughout the study.

6. What Vaccines are Being Tested in HVTN 203?

The ALVAC-HIV (vCP1452) vaccine is made of an attenuated (weakened) canarypox virus that has been genetically altered to contain manmade copies of selected HIV genes. The canarypox virus cannot infect or harm humans. The vaccine is manufactured by Aventis Pasteur of Lyon, France.

The AIDSVAX B/B vaccine consists of manmade, recombinant HIV protein and is provided by the manufacturer, VaxGen of San Francisco, California, USA.

Both vaccines are made according to guidelines reviewed and approved by the U.S. Food and Drug Administration (FDA) for clinical testing.

7. What Does the ALVAC-HIV (vCP1452) Vaccine Contain?

ALVAC-HIV (vCP1452) is made of an attenuated (weakened) canarypox virus that has been genetically altered to contain manmade copies of selected HIV genes: the *env* gene coding for the envelope protein gp120; the *gag* gene coding for the core protein; the portion of the *pol* gene coding for the protease enzyme; and portions of genes expressing other parts of the pol and nef proteins. Scientists chose the canarypox virus to make ALVAC-HIV vaccines such as vCP1452 because: 1) research has shown that the canarypox virus appears to be safe to use in humans; 2) canarypox does not multiply in human cells; and 3) it carries the vaccine genes into the body's cells. **Volunteers CANNOT become infected with HIV from this vaccine.**

8. What Does AIDSVAX B/B Vaccine Contain?

The AIDSVAX B/B vaccine is a manmade, recombinant vaccine consisting of HIV surface protein, gp120, based on two different strains of HIV. Because most neutralizing antibodies in HIV-infected people are directed against the surface proteins (gp120) of HIV, vaccines based on gp120 were among the first developed and are the best studied. The gp120 genes used to make this vaccine were derived from two subtype B viruses, which is the most common subtype in the Americas and Europe. **The vaccine contains NO HIV and volunteers CANNOT become infected with HIV from the gp120 vaccine.**

9. Can These Vaccines Cause HIV Infection?

NO. The AIDSVAX B/B vaccine is synthetic; it is NOT made directly from HIV and cannot cause HIV infection. The ALVAC-HIV (vCP1452) vaccine is made using copies of HIV genes. It is not made directly from HIV and lacks the genes that are absolutely necessary to make HIV. Volunteers cannot become infected with HIV from ALVAC-HIV (vCP1452), nor can they pass the canarypox or the genes it carries onto anyone else.

10. How Do Scientists Think These Vaccines Could Help Prevent HIV/AIDS?

The immune system fights viral infections with two major weapons: neutralizing antibodies and cytotoxic T lymphocytes (CTLs). Neutralizing antibodies are proteins that can block HIV from infecting cells. CTLs, also known as "killer T cells," are white blood cells that can potentially kill cells infected with HIV.

The two vaccines are used to try to stimulate these two different parts of the immune system. ALVAC-HIV (vCP1452) is given to stimulate the body's production of CTLs against HIV. The AIDSVAX B/B is given to stimulate the production of neutralizing antibodies, proteins that block HIV from infecting cells.

The combination of these two different types of vaccines appears to show the most promise among HIV vaccine strategies tested to date for stimulating a broad immune response because each vaccine stimulates a different arm of the immune system.

11. Are These Vaccines Safe?

The safety of these vaccines is closely monitored in all studies. There have been no serious side effects attributable to these vaccines reported in previous trials. The vaccine injections may cause a sore arm, headache or a slight fever in some people for a few days. These symptoms have also been seen in volunteers who receive placebo. Volunteers will have their blood drawn and urine checked for any reactions to the vaccines and to measure their immune responses to the vaccines.

The researchers conducting the study will watch the volunteers closely for any adverse effects of the vaccines. In addition, the study will be monitored by an independent group of experts known as the DAIDS Vaccine and Prevention Data and Safety Monitoring Board. This group will review the information from the study and will pay close attention to any harmful reactions. If the Board decides that significant adverse events have occurred, it can recommend that further injections be delayed or the study be stopped.

12. What is the Design of This Study?

Volunteers will be randomly assigned to one of four study groups.

- Group 1 will have 60 volunteers who receive ALVAC-HIV (vCP1452) alone at 0 and 1 month and both vaccines at the 3 and 6 month visits.
- Group 2 will have 60 volunteers who receive both vaccines at 0, 1 and 6 month and ALVAC-HIV (vCP1452) alone at the 3rd month.
- Group 3 will have 120 volunteers who receive ALVAC-HIV (vCP1452) alone at all four time points.
- Group 4 will have 90 volunteers who receive a placebo at the same time points. A placebo is an inactive substance that has no vaccine or medicine in it. The response of volunteers who receive the placebo will be compared to those who receive the ALVAC-HIV (vCP1452) alone or in combination with AIDSVAX B/B.

All participants will receive an injection in each arm at four time points (0, 1, 3 and 6 months) during the study.

This is a "double-blind" study, which means that no one directly involved in the trial -- neither the volunteers, the study investigators nor the nurses -- knows which group volunteers are in until the study is completed.

13. Have These Vaccines Been Studied Before?

Yes, HVTN 203 is a medium-sized trial built upon the results of previous smaller trials of these vaccines. More than 1,800 volunteers in France, Uganda, Thailand and the United States have received canarypox-based HIV vaccines, and no serious side effects attributable to these vaccines have been reported. ALVAC-HIV (vCP1452) is the most advanced ALVAC-HIV vaccine and has recently been administered to more than 150 participants in the United States and France.

The AIDSVAX B/B vaccine has been extensively studied in the United States, and over the last six years, has been given to more than 5,000 adults, children and newborns in Phase I (small), Phase II (medium) and Phase III (large) studies. The vaccine appears to be safe and well-tolerated.

14. What is Known So Far About How People in Clinical Trials Respond to the ALVAC-HIV and AIDSVAX B/B Vaccines?

In previous trials, both of these vaccines have induced anti-HIV immune responses in most volunteers tested. Volunteers receiving ALVAC alone and in combination with gp120 vaccines have demonstrated a neutralizing antibody response (i.e., their serum was able to inhibit some strains of HIV in a laboratory test). Some volunteers receiving ALVAC alone and in combination developed CTL responses against HIV.
In general, volunteers who received the vaccine combination have a more extensive immune response than the volunteers receiving either of the vaccines alone.

15. Who Reviewed and Approved the Study?

Plans for the study, including the informed consent and protocol, have been reviewed and approved by an independent Institutional Review Board (IRB) responsible for overseeing HIV-related research at each study site. In addition, both the U.S. National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) must review and approve the study. While it is under way, the study will be monitored by an independent group of experts known as the DAIDS Vaccine and Prevention Data and Safety Monitoring Board. This group will periodically review the information from the study and will pay close attention to any harmful reactions. If the Board finds that significant adverse events have occurred, it can recommend that further injections be delayed or the study be stopped.

16. What Safeguards and Ethical Procedures are in Place for Protecting the Volunteers?

Before deciding to enter the study, potential volunteers are provided information about HIV and AIDS, the intent of the study, possible risks and benefits of participation, and study procedures. In addition to the unknown risks associated with any new, experimental vaccine, potential risks include side effects due to injection into a muscle and social issues associated with taking part in HIV studies. Volunteers will be reminded consistently that being part of this study does not mean that they are less likely to become infected with HIV.

Volunteers who are eligible and willing to participate after the study has been fully explained to them will be asked to sign an informed consent form to enroll in the study. Volunteers will be given plenty of time to consider whether they want to participate. Volunteers are free to refuse to join the study or to leave the study at any time without losing the benefits of their standard medical care.

17. Are There Non-Medical Risks?

The ALVAC-HIV (vCP1452)/AIDSVAX B/B vaccine combination causes volunteers to make antibodies to HIV. These volunteers may test antibody positive on a standard HIV screening test, known as an ELISA test. While this effect is transient, this could cause some problems to the volunteer if they were tested for HIV outside of the trial. Several confirmatory tests will be performed to distinguish true HIV infection from vaccine-induced antibody responses. A vaccine-induced antibody positive test would be a good signal that the vaccine is stimulating an immune response.

18. What Will Happen to Volunteers if They Become HIV-Infected from Risky Behavior During the Course of the Study?

Throughout the study, volunteers will receive counseling on HIV prevention. Volunteers will be instructed about the symptoms of early HIV infection and to come to the clinic if such symptoms develop. Clinical and laboratory evaluations will be done periodically throughout the study to determine HIV status. If found to be HIV-infected, a volunteer will be notified in person, as soon as possible, and counseled about what the test results mean and how to avoid passing the virus to others. The volunteer will be referred for medical care, treatment and additional counseling according to standard practices at each site. Testing and counseling will be provided to the volunteer's partner(s), if desired. HIV-infected volunteers will

continue to be followed in the study although they will no longer receive vaccinations.

19. When Might These Vaccines Move On to Phase III/Efficacy Testing?

This study is an important step in a long process leading to efficacy trials. Depending on the results of this study, this vaccine combination might be considered for evaluation in a large-scale, efficacy (Phase III) trial to determine if the combination of these vaccines is effective in preventing HIV infection.

20. How Can I Obtain More Information About the Study?

More information about AIDS vaccine clinical trials can be obtained by calling the AIDS Clinical Trials Information Service (1-800-TRIALS-A) or by visiting their Web site at www.actis.org. More information about the HIV Vaccine Trials Network (HVTN) can be found on their Web site at www.scharp.org/hvtn/.

[Note to Study Sites: Please add your local contact information for recruitment and media requests here.]